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Press release

Buvidal® Weekly and Buvidal® Monthly (CAM2038) approved in Australia as the first long-acting treatment of opioid dependence

Lund, Sweden — 28 November 2018 — Camurus announced today that the Australian Therapeutic Goods Administration (TGA) has approved the company's lead products Buvidal® Weekly and Buvidal® Monthly (CAM2038) for maintenance treatment of opioid dependence within a framework of medical, social and psychosocial support.

"Opioid dependence and non-medical opioid use are large and growing issues in Australia with significant negative impact on individuals, their families and the wider community," said Fredrik Tiberg, President and CEO of Camurus. "Today's approval of Buvidal Weekly and Buvidal Monthly will for the first time give Australian patients access to a long-acting buprenorphine treatment for opioid dependence with a meaningful clinical benefit recognized by the TGA.

Formulated with Camurus' proprietary FluidCrystal® injection depot technology, Buvidal is a lipid-based solution which, once injected, transforms into a nanostructured gel-like depot. The depot slowly biodegrades over time, releasing buprenorphine which blocks the drug-liking effect of opioids in the brain and reduces withdrawal, craving and patient's use of illicit opioids.[1-4]

"The introduction of Buvidal represents the most significant development in over 15 years of opioid dependence treatment in Australia. The flexibility of weekly and monthly injection depots will make treatment much more convenient for patients, reducing the costs and inconvenience of daily dosing, and should serve to lessen the stigma experienced by many patients," said Professor Nicholas Lintzeris, Director of Drug & Alcohol Services, South East Sydney Local Health District and the Division of Addiction Medicine, Central Clinical School, University of Sydney.[5]

The TGA approval of Buvidal Weekly and Buvidal Monthly is based on safety and efficacy data from a global development program comprising seven clinical studies, including a randomized, double-blind, double-dummy, active controlled Phase 3 study in 428 patients with opioid dependence. Results from this study demonstrated improved treatment outcomes with Buvidal compared to daily standard treatment with sublingual buprenorphine/naloxone.[4]

The Australian approval follows the recent European Commission approval of Buvidal®, announced 22 November 2018. In the US, the Food and Drug Administration has issued a PDUFA goal date of 26 December 2018 for CAM2038 to Camurus' US partner Braeburn.

About opioid dependence
Opioid dependence is an escalating global health problem, contributing to significant

mental, physical and social adverse consequences that include transmission of infectious diseases, criminal activity and incarceration, and unintentional overdose and death.[6]

Opioid use is a serious public health issue in Australia with an estimated 460,000 people aged over 14 years having used opioids – including morphine, oxycodone, methadone and heroin – for non-medical purposes at some time.[7] Of these, 230,000 had used heroin.[7] In 2016, 1,808 drug-induced deaths were registered in Australia, the highest number of drug deaths in 20 years.[8] On a sample day in 2017, approximately 50,000 people in Australia received pharmacotherapy treatment for opioid dependence.[9]

About Buvidal Weekly and Buvidal Monthly (CAM2038)

Buvidal Weekly and Buvidal Monthly (modified release solution for subcutaneous injection) has been developed for the treatment of opioid dependence within a framework of medical, social and psychological treatment. Buvidal is designed for flexible weekly and monthly dosing, allowing tailored treatment to the patient's individual needs. Each injection should be administered by a health care professional.

The TGA approval of Buvidal Weekly and Buvidal Monthly is based on a clinical program with seven clinical studies, including a randomized, double-blind, double-dummy, active controlled Phase 3 study in 428 patients with opioid dependence. In this pivotal study, Buvidal was shown to be at least as effective as effective as standard treatment with daily buprenorphine/naloxone for the primary endpoint of the mean percent urines negative for illicit opioids (35.1% versus 28.4%, p<0.001). Superiority was met for the key secondary endpoint of cumulative distribution function (CDF) for the percent urine tests negative for illicit opioid use (p=0.008). The median CDF was 26.7% for Buvidal and 6.7% for sublingual buprenorphine/naloxone.[4] The safety profile of Buvidal was comparable to sublingual buprenorphine/naloxone, except for mild to moderate injection site reactions.

Formulated with Camurus' FluidCrystal injection depot technology, Buvidal is presented ready for use in pre-filled syringes for administration as small dose volume subcutaneous injection through a thin, 23-gauge needle. Buvidal has been developed for room temperature storage.

About Camurus

Camurus is a Swedish research-based pharmaceutical company committed to developing and commercialising innovative and differentiated medicines for the treatment of severe and chronic conditions. New drug products with best-in-class potential are conceived based on the company's proprietary FluidCrystal drug delivery technologies and its extensive R&D expertise. Camurus' clinical pipeline includes products for the treatment of cancer, endocrine diseases, pain and addiction, which are developed in-house and in collaboration with international pharmaceutical companies. The company's shares are listed on Nasdaq Stockholm under the ticker CAMX. For more information, visit www.camurus.com.

PBS information: Buvidal is not listed on the PBS.

Important safety information

RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS INJECTION: Serious harm or death could result if administered intravenously. Buvidal Weekly and Monthly forms a gel depot upon contact with body fluids and may cause occlusion, local tissue damage and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. CONTRAINDICATIONS: Hypersensitivity to buprenorphine or to any of the excipients, children less than 16 years of age, severe respiratory insufficiency, severe

hepatic insufficiency (Child-Pugh C), acute alcoholism or delirium tremens, pregnancy, lactation. SPECIAL WARNINGS AND PRECAUTIONS FOR USE: General: Opioids may cause orthostatic hypotension in ambulatory patients. Opioids should be used with caution in patients with: head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure, hypotension, prostatic hypertrophy or urethral stenosis, myxoedema, hypothyroidism, or adrenal cortical insufficiency (eg Addison's disease), dysfunction of the biliary tract; the elderly or debilitated. Opioid-induced miosis, changes in the level of consciousness or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. Misuse, abuse and diversion: Buprenorphine is subject to misuse, abuse and diversion, similar to other opioids, legal or illicit. Buvidal must be administered directly to the patient by a healthcare professional. Buvidal should not be made available directly to patients. Monitor patients carefully for progression of opioid dependence and drug use. Respiratory depression: Buprenorphine should be used with care in patients with respiratory insufficiency (eg chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). The use of buprenorphine is contraindicated in patients with severe respiratory insufficiency. Buprenorphine may cause severe, possibly fatal, respiratory depression in children and non-dependent persons who accidentally or deliberately ingest it. CNS depression: Buprenorphine may cause drowsiness particularly when taken together with alcohol or central nervous system depressants such as benzodiazepines, tranquillisers, sedatives, gabapentinoids or hypnotics. Dependence: Buprenorphine is a partial agonist at the μ (mu)-opioid receptor and chronic administration can produce opioid dependence. Use in hepatic impairment: Buprenorphine should be used with caution in patients with moderate hepatic impairment. The use of buprenorphine is contraindicated in patients with severe hepatic insufficiency. Use in renal impairment: Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min). INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS: Buprenorphine should be used cautiously when co-administered with: benzodiazepines, gabapentinoids, alcoholic or medications containing alcohol, other central nervous system depressants: other opioid derivatives; certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances, opioid analgesics, naltrexone and nalmefene, CYP3A4 inhibitors and inducers, monoamine oxidase inhibitors (MAOI). PREGNANCY AND LACTATION: Use in pregnancy – Pregnancy Category C: Buvidal is contraindicated in pregnant women Use in lactation: Buvidal should not be used in breast-feeding women. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Patients should be cautioned about operating hazardous machinery in case buprenorphine may affect their ability to engage in such activities. ADVERSE EFFECTS: The adverse events most frequently reported in the double-blind, pivotal phase 3 efficacy clinical trial were constipation, symptoms commonly associated with drug withdrawal, such as headache, nausea, insomnia and vomiting, injection site related events such as injection site pain, injection site pruritus and injection site erythema, urinary tract infection and upper respiratory tract infection. Adverse reactions reported with buprenorphine: The following adverse reactions have been reported with the use of buprenorphine products and may occur with Buvidal. Very common: Insomnia, headache, nausea, hyperhidrosis, drug withdrawal syndrome, and pain. Common: Bronchitis, infection, influenza, pharyngitis, rhinitis, lymphadenopathy, decreased appetite, agitation, anxiety, depression, hostility, nervousness, paranoia, thinking abnormal, dizziness, hypertonia, migraine, paraesthesia, somnolence, syncope, tremor, lacrimal disorder, mydriasis, palpitations, vasodilatation, cough, dysnpoea, yawning, abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia,

gastrointestinal disorder, flatulence, vomiting, rash, arthralgia, back pain, bone pain, muscle spasms, myalgia, neck pain, dysmenorrhoea, asthenia, chest pain, chills, malaise, oedema peripheral and pyrexia. OVERDOSE: Respiratory depression, as a result of central nervous system depression, is the primary symptom requiring intervention in the case of buprenorphine overdose because it may lead to respiratory arrest and death. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. Use of an opioid antagonist (ie naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents. The long duration of action of buprenorphine and the modified release from Buvidal, should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms. For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia) for advice.

Notes and references

1. *Haasen C, Linden M, Tiberg F. Pharmacokinetics and pharmacodynamics of a buprenorphine subcutaneous depot formulation (CAM2038) for once-weekly dosing in patients with opioid use disorder. J Subst Abuse Treat 2017; 78:22–29.*
2. *Albayaty M, Linden M, Olsson H, Johnsson M, Strandgården K, Tiberg F. Pharmacokinetic evaluation of once-weekly and once-monthly buprenorphine subcutaneous injection depots (CAM2038) versus intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade: an open-label Phase 1 study. Adv Ther 2017; 34(2):560–575.*
3. *Walsh SL, Comer SD, Lofwall MR, Vince B, Levy-Cooperman N, Kelsh D, et al. Effect of buprenorphine weekly depot (CAM2038) and hydromorphone blockade in individuals with opioid use disorder: a randomized clinical trial. JAMA Psychiatry 2017; 74(9):894–902.*
4. *Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: A randomized clinical trial. JAMA Intern Med 2018; 178(6)764–773.*
5. *Dr. Lintzeris is an investigator in the Buvidal clinical program which was sponsored by Braeburn and Camurus. In relation to this media announcement, no compensation was provided to Dr Lintzeris, and the opinions expressed are his own. Dr Lintzeris has been briefed by Camurus on the approved use of this product.*
5. *World Drug Report 2018, United Nations June 2018 https://www.unodc.org/wdr2018/ Accessed November 2018.*
6. *National opioid pharmacotherapy statistics (NOPSAD) 2016. https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/national-opioid-pharmacotherapy-statistics-nopsad-2016/contents/introduction Accessed November 2018.*
7. *Australian Bureau of Statistics. Causes of death, Australia 2016. Drug Induced Deaths in Australia: A changing story. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2016~Main%20Features~Drug%20Induced%20Deaths%20in%20Australia~6 Accessed November 2018.*
8. *National opioid pharmacotherapy statistics (NOPSAD) 2017. https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/nopsad-2017/contents/summary Accessed November 2018.*

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